PATENT SPECIFICATION (11) 1347935

1347935

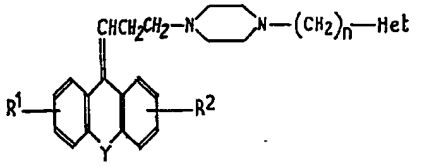
(21) Application No. 16282/72 (22) Filed 7 April 1972
(31) Convention Application No. 22549 (32) Filed 10 April 1971 in
(33) Japan (JA)
(44) Complete Specification published 27 Feb. 1974
(51) International Classification C07D 99/02; A61K 27/00; C07D 99/04, 99/06
(52) Index at acceptance
C2C 170—189—276 171—178—185 173—197—288 174—176—180 174—271—276 175—193—286 178—191—287 179—194—273 180—188—286 185—191—277 200 213 215 226 22X 22Y 246 247 250 251 252 253 254 25Y 28X 29X 29Y 30Y 313 31Y 337 338 357 373 37Y 3A13C10H 3A13C1C 43X 551 55X 614 77X 790 79Y QL YX ZB ZD

(19)

(54) PIPERAZINE DERIVATIVES, METHODS FOR THEIR PRODUCTION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(71) We, YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD., a Japanese Company, of 35, Hirano-Machi 3-Chome, Higashi-Ku, Osaka, Japan, do hereby declare the invention for which we pray that patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

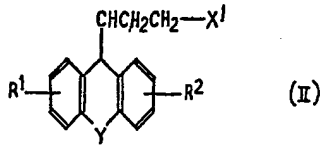
This invention relates to novel and therapeutically valuable piperazine derivatives of the general formula:



(I)

and pharmaceutically acceptable acid addition salts thereof, wherein Y is the group $-CH_2-O-$, $-CH_2-S-$, $-CH_2-SO_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-C(CH_3)_2-$, $-O-$ or $-S-$, each of R^1 and R^2 is a hydrogen or halogen (e.g. F, Cl or Br) atom, an alkyl group of 1 to 4 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl or tertiary butyl) or a methoxy or methylthio group, Het represents furyl, pyridyl or thienyl and n is 0, 1, 2 or 3.

The compounds (I) can be produced by reacting a compound of the general formula:



(II)

with a compound of the general formula:

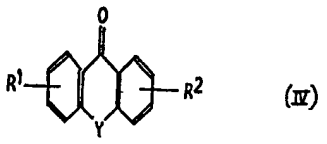
$$X^2-(CH_2)_n-Het \qquad (III)$$

wherein one of X^1 and X^2 is an atom or radical capable of reacting with the other such group, such as halogen (e.g. Cl, Br or I) or sulfonyloxy (such as methylsulfonyloxy, phenylsulfonyloxy or *p*-tolylsulfonyloxy), and the other is 1-piperazinyl.

The reaction is advantageously carried out in a solvent at a temperature of from room temperature to reflux temperature for several to twenty hours. The said solvent may be selected from benzene, toluene, xylene, ethanol, dioxane, pyridine, acetone, dimethylformamide, dimethylsulfoxide and water and mixtures thereof.

The reaction may be carried out in the presence of a deacidifying or condensing agent such as sodium hydroxide, sodium carbonate, potassium carbonate, triethylamine, pyridine or potassium iodide.

The starting compounds (II) can be produced from a compound of the formula:



(IV)

[*Price 25p*]

by the methods disclosed in Journal of Organic Chemistry, Vol. 27, p. 4134 (1962) and Canadian Patent No. 717,977 [Chemical Abstracts, Vol. 64, 3443b (1966)].

The starting compounds of formula (II) may be obtained as a mixture of two isomers (cis and trans). These isomers may be separated in a conventional manner. However, the separation is not necessary, since the compounds of formula (I) are therapeutically effective also in the form of a mixture of the two corresponding isomers.

The compounds of formula (I) can be converted into acid addition salts in a conventional manner by treatment with various inorganic and organic acids, for example, hydrochloric, sulfuric, maleic, fumaric and tartaric acid.

The compounds of formula (I) and pharmaceutically acceptable acid addition salts thereof are excellent in anticonvulsant effect, antimetrazole effect, suppression of fighting behavior and antimescaline effect as shown, for example, by the following tests.

(i) Anticonvulsant effect

The test compound was intraperitoneally administered to one group of 6 dd-strain male mice each weighing 20—25 g. After an hour, a silver electrode of an electroshock seizure apparatus [designed by L. A. Woodbury et al.: see, Archives Internationales de Pharmacodynamie et de Therapie, vol. 42, pp. 72—102 (1952)] was brought into contact with the cornea and an alternating current (2000 volts, 12.5 milliamperes) was applied for 0.2 second to induce convulsion. The ED_{50}, the dose required to lower the seizure rate by 50% against the control mice, was determined from the dose-effect correlation curve.

(ii) Antimetrazole effect

Metrazole (pentylenetetrazole) (150 mg/kg) was administered subcutaneously to groups each consisting of 6 mice 15 minutes after the intraperitoneal administration of the test compound. The number of dead mice was counted 30 minutes after the administration of metrazole, and then the ED_{50}, the dose required to suppress the death rate to 50%, was determined.

(iii) Suppression of Fighting Behavior

Fighting episodes were produced in mice by the method described by Tedeschi et al. in Journal of Pharmacology and Experimental Therapeutics, vol. 125, p. 28 ff. (1959). Groups of 8 female mice (4 pairs) were given the test compound orally 60 minutes prior to receiving electric foot-shock for 3 minutes with an interrupted direct current of 530 volts, 1.3 milliamperes, 10 cycles per second. In case 3 fighting episodes or less within 3 minutes were exhibited, the pair of mice was deemed to be suppressed by the test compound. The control mice of 81 pairs showed the fighting episodes of 8.7 times on the average under the same conditions. The ED_{50}, the dose required to suppress 50% of fighting pairs, was determined graphically.

(iv) Antimescaline effect

A modification of the method of R. A. Turner [Screening Method in Pharmacology, Edited by R. A. Turner, p. 73, Academic Press (1965)] was used to study the prevention of scratching episodes induced by mescaline. The test compounds were given to groups each of 6 female mice orally 60 minutes prior to treatment with mescaline sulfate (30 mg/kg intraperitoneal). Ten minutes later, the effect of test compounds on the scratching episodes was observed for 10 minutes. The ED_{50} shows the dose required for prevention of scratching in 50% of the animals.

Results:

Compound	Anticonvulsant effect, ED_{50} mg/kg (intraperitoneal)
A	40
B	90
C	40
D	23
E	28
F	17

Compound	Antimetrazole effect, ED_{50} mg/kg (intraperitoneal)
A	15
B	20
C	42
D	17
E	45
F	70

Compound	Suppression of Fighting Behavior, ED_{50} mg/kg (oral)
A	150
B	44
C	28
D	23
E	6
F	40

Compound	Antimescaline effect, ED_{50} mg/kg (oral)
A	0.3
B	4.2
C	5.0
D	20.0
E	6.0
F	6.0

Compounds A to F are identified below:

A: 11 - [3 - (4 - (3 - pyridylmethyl) - 1-piperazinyl)propylidene] - 6,11 - dihydrodibenz[b,e]oxepin trihydrochloride (hydrate)

B: 11 - [3 - (4 - (2 - pyridylmethyl) - 1-piperazinyl)propylidene] - 6,11 - dihydrodibenz[b,e]oxepin dimaleate

C: 11 - [3 - (4 - (4 - pyridylmethyl) - 1-piperazinyl)propylidene] - 6,11 - dihydrodibenz[b,e]oxepin trihydrochloride (hydrate)

D: 5 - [3 - (4 - (2 - (4 - pyridyl)ethyl)-1 - piperazinyl)propylidene] - 10,11-dihydro - dibenz[a,d]cycloheptene trihydrochloride (hydrate)

E: 5 - [3 - (4 - (2 - pyridylmethyl) - 1-piperazinyl)propylidene] - 10,11 - dihydrodibenz[a,d]cycloheptene trihydrochloride (1/2 hydrate)

F: 5 - [3 - (4 - (3 - pyridylmethyl) - 1-piperazinyl)propylidene] - dibenz-[a,d] - cycloheptene trihydrochloride (1/2 hydrate)

In view of various tests including those mentioned above, the compounds of the invention represented by formula (I) and pharmaceutically acceptable acid addition salts thereof can be administered safely as psychotropic agents for the treatment of neuroses, schizophrenia, mania, depression and epilepsy, in the form of a pharmaceutical preparation with a suitable and conventional carrier or adjuvant, administrable orally, without harm to the patients.

The pharmaceutical preparations can take any conventional form such as tablets, capsules or powders.

Formulation Examples:

10 mg tablets are prepared from the following compositions:

Compound A	10 mg
Lactose	68
Starch	20
Microcrystalline Cellulose	20
Methyl Cellulose	1
Magnesium Stearate	1
	120 mg

25 mg tablets are prepared from the following compositions:

Compound A	25 mg
Lactose	53
Starch	35
Microcrystalline Cellulose	35
Methyl Cellulose	1
Magnesium Stearate	1
	150 mg

10% powders are prepared from the following compositions:

Compound A	10%
Lactose	70
Starch	19
Methyl Cellulose	1
	100%

The oral daily dose of compound (I) or a salt thereof for human adults usually ranges from about 30 to 150 milligrams, in single or multiple dose, but it may be changed depending upon the age and/or symptoms of the patients.

The present invention will be better understood from the following examples which are illustrative and not limitative of the present invention. Percentages are by weight.

Example 1.

A mixture of 7 g of 11 - (3 - bromopropylidene) - 6,11 - dihydro - dibenz[b,e]-oxepin, 4.9 g of 1-(2-thenyl)piperazine, 4.5 g of potassium carbonate, 30 ml of toluene and 30 ml of dimethylformamide is heated at 110—120°C with stirring for 7 hours. After cooling, water is added to the reaction mixture, the whole is extracted with toluene and the toluene layer is washed with water. A stoichiometrically slightly excessive amount of concentrated hydrochloric acid is added to the toluene layer, and the whole is shaken. A jelly-like substance is liberated. The toluene liquor is removed by decantation, and isopropyl alcohol is added to the jelly to cause crystallization. Recrystallization from 80% methanol gives 6.5 g of 11-[3 - (4 - (2 - thenyl) - 1 - piperazinyl)propylidene] - 6,11 - dihydro - dibenz[b,e]oxepin dihydrochloride melting at 257—258°C (decomposition).

Example 2.

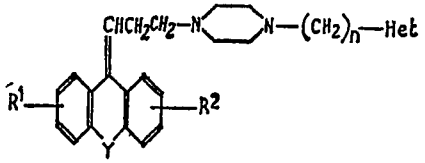
A mixture of 6.2 g of 11 - [3 - (1 - piperazinyl)propylidene] - 6,11 - dihydrodibenz-[b,e]oxepin, 3 g of 2-thenylchloride, 3.5 g of potassium carbonate and 70 ml of acetone is refluxed for 3 hours. The acetone is distilled off, water is added, and the mixture is extracted with toluene. The work-up procedure described in Example 1 gives 5.5 g of 11 - [3-(4 - (2 - thenyl) - 1 - piperazinyl)propylidene]-6,11 - dihydro - dibenz[b,e]oxepin dihydrochloride melting at 257—258°C (decomposition).

Example 3.

A mixture of 8 g of 11 - (3 - bromopropylidene) - 6,11 - dihydro - dibenz[b,e]oxepin, 4 g of 1 - (3 - pyridylmethyl)piperazine, 4 g of potassium carbonate, 30 ml of toluene and 30 ml of dimethylformamide is heated at 110—120°C with stirring for 7 hours. After cooling, water is added to the reaction mixture, and the

whole is extracted with toluene. The extract is washed with water, and extracted with dilute hydrochloric acid. The aqueous extract is made alkaline with potassium carbonate, and the liberated oil is extracted with chloroform. The chloroform is removed, and the oily residue is dissolved in 30% ethanolic hydrochloric acid. After removal of the ethanol by distillation, isopropanol and a little amount of water are added to the solution to cause crystallization. Recrystallization of the product from 80% ethanol gives 6 g of 11 - [3 - (4 - (3 - pyridyl-methyl) - 1 - piperazinyl)propylidene] - 6,11-dihydro-dibenz[b,e]oxepin trihydrochloride monohydrate melting at 237°C (decomposition).

Using the procedure set forth in the above examples, but substituting equivalent amounts of the appropriate starting materials, the following compounds are also produced:



Example	Y	R^1	R^2	n	Het	Salt and m.p. (°C)
4	—CH_2—O—	H	H	1	2-furyl	2 maleate 184—186
5	—CH_2—O—	H	H	1	4-pyridyl	3 HCl H_2O 240 (d*)
6	—CH_2—O—	H	H	1	2-pyridyl	2 maleate 172 (d*)
7	—CH_2—O—	H	2-Cl	1	2-pyridyl	2 HCl 264—265 (d*)
8	—CH_2—O	H	2-Cl	1	3-pyridyl	3 HCl 259—261 (d*)
9	—CH_2—O—	H	2-CH_3	1	4-pyridyl	3 HCl H_2O 254 (d*)
10	—CH_2—O—	H	H	2	2-pyridyl	3 HCl $\frac{1}{2}$ H_2O 177—180(d*)
11	—CH_2—O—	H	H	2	4-pyridyl	3 HCl H_2O 198—200 (d*)
12	—CH_2—O—	H	2-OCH_3	2	4-pyridyl	3 HCl H_2O 184—185 (d*)
13	—CH_2—O—	H	2-Cl	2	4-pyridyl	3 HCl H_2O 223—225 (d*)
14	—CH_2—O—	H	H	0	2-pyridyl	2 maleate 145 (d*)
15	—CH_2—S—	H	H	1	2-thienyl	2 HCl 255—257 (d*)

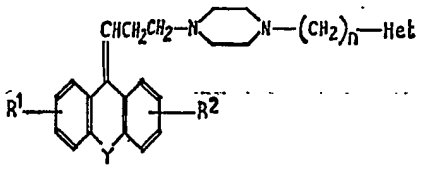
Example	Y	R^1	R^2	n	Het	Salt and m.p. (°C)
16	$-CH_2-S-$	H	H	2	4-pyridyl	3 HCl 145 (d*)
17	$-CH_2-SO_2-$	H	H	2	4-pyridyl	3 maleate 147—149
18	$-CH_2-CH_2-$	H	H	1	2-pyridyl	3 HCl $\frac{1}{2}$ H_2O 235 (d*)
19	$-CH_2-CH_2-$	H	3-Cl	1	4-pyridyl	3 HCl H_2O 241 (d*)
20	$-CH_2-CH_2-$	H	3-CH_3	1	2-pyridyl	3 HCl H_2O 237 (d*)
21	$-CH_2-CH_2-$	H	H	1	4-pyridyl	3 HCl 236 (d*)
22	$-CH_2-CH_2-$	H	H	2	4-pyridyl	3 HCl H_2O 192 (d*)
23	$-CH=CH-$	H	H	1	3-pyridyl	3 HCl $\frac{1}{2}$ H_2O 249 (d*)
24	$-CH=CH-$	H	H	2	4-pyridyl	3 maleate 158 (d*)
25	$-C(CH_3)_2-$	H	H	1	2-thienyl	2 HCl 267 (d*)
26	—O—	H	2-OCH_3	1	4-pyridyl	3 maleate 125
27	—S—	H	2-SCH_3	1	4-pyridyl	3 HCl H_2O 225 (d*)

d*: decomposition.

The thus obtained compounds (acid addition salts) could be converted into their corresponding free bases in conventional manner.

WHAT WE CLAIM IS:—

1. N-substituted piperazine compounds of the general formula:



wherein Y represents the group $-CH_2-O-$, $-CH_2-S-$, $-CH_2-SO_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-C(CH_3)_2-$, $-O-$ or $-S-$, each of R^1 and R^2 represents a hydrogen or halogen atom, an alkyl group of 1 to 4 carbon atoms or a methoxy or methylthio group, n is 0, 1, 2 or 3 and Het represents a furyl, pyridyl or thienyl group.

2. 11 - [3 - (4 - (3 - Pyridylmethyl) - 1-piperazinyl)propylidene] - 6,11 - dihydrodibenz[b,e]oxepin.

3. 11 - [3 - (4 - (2 - Pyridylmethyl) - 1-piperazinyl)propylidene] - 6,11 - dihydrodibenz[b,e]oxepin.

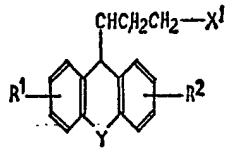
4. 11 - [3 - (4 - (4 - Pyridylmethyl) - 1-piperazinyl)propylidene] - 6,11 - dihydrodibenz[b,e]oxepin.

5. 5 - [3 - (4 - (2 - (4 - Pyridyl)ethyl) - 1-piperazinyl)propylidene] - 10,11 - dihydrodibenz[a,d]cycloheptene.

6. 5 - [3 - (4 - (2 - Pyridylmethyl) - 1-piperazinyl)propylidene] - 10,11 - dihydrodibenz[a,d]cycloheptene.

7. 5 - [3 - (4 - (3 - pyridylmethyl) - 1-piperazinyl)propylidene] - dibenz[a,d]cycloheptene.

8. A method of preparing a compound as defined in claim 1, which comprises reacting a compound of the general formula:



(II)

with a compound of the general formula:

$$X^2-(CH_2)_n-Het \qquad (III)$$

wherein one of X^1 and X^2 is a 1-piperazinyl group and the other is an atom or radical capable of reacting with the 1-piperazinyl group and Y, R^1, R^2, Het and n are as defined in claim 1.

9. A method as claimed in claim 8, substantially as hereinbefore described in any of the foregoing Examples.

10. A compound prepared by a method as claimed in claim 8 or 9.

11. A pharmaceutically acceptable acid addition salt of a compound as claimed in any of claims 1 to 7 or 10.

12. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 7, 10 or 11 in admixture with a pharmaceutically acceptable inert carrier therefor, said compound being present in a psychotherapeutically effective amount.

13. A composition as claimed in claim 12, substantially as hereinbefore described.

GEE & CO.,
Chartered Patent Agents,
51/52, Chancery Lane, London, WC2A 1HL,
Agents for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1974.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.